UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,594	12/13/2004	Monika Baudler	26541U	9121

34375 7590 09/26/2007
NATH & ASSOCIATES PLLC
112 South West Street
Alexandria, VA 22314

EXAMINER	
RAO, DEEPAK R	
ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,594	BAUDLER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050310*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula 1 and the corresponding salt thereof, does not reasonably provide enablement for a hydrate, solvate, hydrate of the salt or solvate of the salt of a compound of formula 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factual Basis:

A. Specification has no working example of **hydrate**, **solvate, hydrate of a salt** or **solvate of a salt** of compound of formula 1; and some of the exemplified compounds within the claimed genus were in contact with a solvent and/or water. Yet they have not formed solvate as evident form spectral data provided for these compounds.

B. Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

Scope of enablement rejection:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula 1 or a salt thereof, or hydrate, solvate, hydrate of a salt or solvate of a salt thereof. Specification is not adequately enabled as to how to make solvate of compounds of formula 1. Specification has no example of solvate or hydrate of the instant compounds. Specification on page 16 recites that 'the compounds when isolated in crystalline form, can contain various amounts of solvents' but there is no enabling disclosure of such solvates or hydrates when the crystalline form contains water.

The compound of formula 1 embrace substituted pyrimidine compounds substituted with variable groups R1, R2, R3, etc. Careful calculation of the number of compounds embraced in the instant formula 1 shows a large number of compounds. The term "substituted" embraces undefined number of variable groups and thus, the genus embraced by the claims is excessively large and there is no teaching of any solvate or hydrate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that

is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors,

hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

2. **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to hydrates or solvates. There is no example of hydrate or solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

4. **The presence or absence of working examples:**

Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures and other parameters. The experimentation is potentially open-ended. The direction concerning the solvates and hydrates is found on page 16, which simply states that 'the invention also comprises solvates and hydrates', however, there is no working example of any hydrate or solvate formed.

The instant claims are drawn to hydrate or solvate, yet the numerous examples presented all failed to produce a solvate or even hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claims would lead to desired solvate of the compound of formula 1. As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula 1 embraced in the instant claims in view of the pertinent reference teachings.

2. Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating asthma, does not reasonably provide enablement

for a method of treating all of the diseases or disorders recited in claim 17, such as an acute and/or chronic airway disorder, an inflammatory or allergen-induced airway disorder, bronchitis, obstructive bronchitis, ... other proliferative, inflammatory, allergic skin disorders, a disorder in connection with disturbances of brain metabolism, disorders of the central nervous system, ... arteriosclerotic dementia, cancer and diabetic insipidus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims 17-18 are drawn to 'a method of treating a patient afflicted with a disease or disorder' and lists a large list of assorted diseases and disorders having diverse mechanisms or modes of action. The specification at pages 25-26 provides *in vitro* assays to measure the PKC-theta (PKC-θ) inhibition and IC_{50} values for some of the exemplified compounds are provided. The specification, however, does not provide how the test data correlates to the diverse diseases or disorders of the instant claims. The instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic,

receptor binding or enzymatic functionality and thereby reach through to many diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification at pages 25-26, are related to PKC-theta inhibition in standard enzyme assays. Applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of PKC-θ. A recent reference, Hayashi et al. (Pharmacological Research 2007), regarding PKC-theta provides that: "However, in order to fully realize the potential of PKCθ as a drug target, it would be important to elucidate the mechanisms that control the activation and unique localization of PKCθ, including the regulatory function of its C2-like domain, identify its physiological substrates, and expand the analysis of the effects of PKCθ deletion to additional models of immunologically relevant diseases" (see page 543). Thus, the reference provides the importance of elucidating the mechanisms surrounding PKCθ.

The specification discloses that the compounds are useful as inhibitors of PKC-theta and therefore, useful to treat a large list of diverse diseases. There is nothing in the disclosure regarding how the *in vitro* test data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include HIV-infection, rheumatoid arthritis, proliferative, inflammatory, allergic skin disorders, CNS

disorders, cancer, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

Enablement for the scope of "treating inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the

response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The instant claims include 'a method for the treatment of cancer' and the terms 'cancer' and 'proliferative disorders' represent anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. The state of the art is not indicative any pharmaceutical agents that are useful in the treatment of cancer generally. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The instant claims are directed to method of treatment of diseases including those associated with HIV infection. However, the specification does not sufficiently establish that the instant compounds can be used in the methods as claimed. The biological test assays are provided in the specification pages 25-26 to determine the *PKCθ* inhibitory activity of the

compounds and there is insufficient evidence that such studies correlate with *in vivo* efficacy in treatment of all diseases including those associated with HIV in humans. The obstacles to therapy of HIV are well documented in the literature, which include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus; and 2) the complexity and variation of the pathology of HIV infection in different individuals.

It is disclosed in the specification that the claimed compounds are useful for 'treatment of CNS disorders', which cover diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that 'some degenerative diseases are difficult to classify because they involve multiple anatomic locations' (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that '[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease' (pg. 1994).

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or

prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims, in the definition of 'aryl' the recitation "**and mixtures thereof**" (all occurrences) is confusing and indefinite. It is not clear what types of **mixtures** are intended. The discrepancy is observed through out the claims following the definition 'aryl' in each claim.
2. In claim 17, in the recitation - "**other** proliferative, inflammatory, allergic skin disorders" it is not clear what is intended by the term 'other' and what 'other disorders' are intended.
3. Claim 19, the terms "**derivative**" (see line 4) and "**derivate**" (see line 6) may be interpreted as a residue derived from the compounds or a modification to the compounds recited in the claims, and it is confusing which compounds are derived from or modified to, from the other ingredients or compounds recited in the claims.

Receipt is acknowledged of the Information Disclosure Statement filed on March 10, 2005 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

September 18, 2007